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Authors

Brandon, Mark P
Koenig, Julie
Leutgeb, Stefan

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Parallel and convergent processing in grid cell, head-direction cell, boundary cell, and place cell networks

Mark P. Brandon,¹ Julie Koenig^{1†} and Stefan Leutgeb^{1,2*}

The brain is able to construct internal representations that correspond to external spatial coordinates. Such brain maps of the external spatial topography may support a number of cognitive functions, including navigation and memory. The neuronal building block of brain maps are place cells, which are found throughout the hippocampus of rodents and, in a lower proportion, primates. Place cells typically fire in one or few restricted areas of space, and each area where a cell fires can range, along the dorsoventral axis of the hippocampus, from 30 cm to at least several meters. The sensory processing streams that give rise to hippocampal place cells are not fully understood, but substantial progress has been made in characterizing the entorhinal cortex, which is the gateway between neocortical areas and the hippocampus. Entorhinal neurons have diverse spatial firing characteristics, and the different entorhinal cell types converge in the hippocampus to give rise to a single, spatially modulated cell type—the place cell. We therefore suggest that parallel information processing in different classes of cells—as is typically observed at lower levels of sensory processing—continues up into higher level association cortices, including those that provide the inputs to hippocampus. © 2013 The Authors. *WIREs Cognitive Science* published by John Wiley & Sons, Ltd.

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INTRODUCTION

Many of the cortical and hippocampal areas that are required for episodic memory function are also specialized for spatial processing. The shared anatomical substrates for memory and

spatial processing have resulted in the notion that these two cognitive functions use similar neural computations.^{1–3} For example, remembering past events in rich detail requires information from many sensory processing streams to be merged during learning. This is achieved through a cortical hierarchy in which information from primary sensory cortices first converges within higher association areas and then within the entorhinal cortex and hippocampus.⁴ Similarly, the emergence of spatial firing patterns also requires the convergence of information from many different sensory systems. A standard functional–anatomical model has emerged in which information from higher visual, auditory, somatosensory, and olfactory association cortices

*Correspondence to: sleutgeb@ucsd.edu

¹Neurobiology Section and Center for Neural Circuits and Behavior, Division of Biological Sciences, University of California, San Diego, La Jolla, CA, USA

²Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA, USA

[†]Present address: Center for Functional Connectomics, Korean Institute of Science and Technology, Seoul, Republic of Korea

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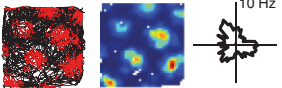
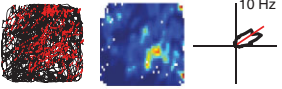
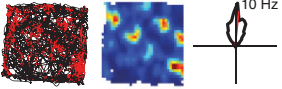
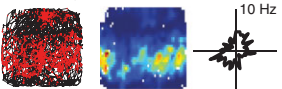
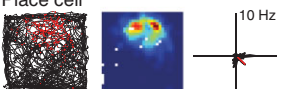
	Pre-Parasubiculum	MEC II	MEC III	MEC V-VI	Hippocampus
Grid cell 	✓	✓	✓	✓	NO
Head direction cell 	✓	NO	✓	✓	NO
Conjunctive cell 	✓	NO	✓	✓	NO
Boundary vector cell 	✓	✓	✓	✓	NO
Place cell 	NO	NO	NO	NO	✓

FIGURE 1 | Examples of cell types with spatial tuning in the hippocampus and in parahippocampal cortices. The left column displays data from each cell type during exploration of an open field arena. Within this column, the spatial selectivity of each cell type is shown by plotting the location of each spike (in red) onto the trajectory of the animal (in black). The central panels are color-coded firing rate maps of the same arena with high firing rates in red and low firing rates in blue. Finally, the right panels are polar plots showing firing rate as a function of the head direction of the animal during exploration in the environment. The right columns indicate in which regions each spatially tuned cell type is found. Grid cells fire in multiple spatial locations that form a triangular 'grid' of the environment. Grid cells are found in the presubiculum, parasubiculum, and all layers of the medial entorhinal cortex. Head-direction cells fire throughout the environment but only when the animal is facing a specific direction. Head-direction cells are found in the presubiculum, parasubiculum, and layers III, V, and VI of the medial entorhinal cortex. Conjunctive cells fire in a triangular grid pattern only when the animal is facing a specific direction. Similar to head-direction cells, conjunctive cells are found in the presubiculum, parasubiculum and layers III, V, and VI of the medial entorhinal cortex. Boundary/border cells fire when the animal is located at a specific distance from a wall in the environment. These cells are found in the subiculum (not shown), presubiculum, parasubiculum, and all layers of the medial entorhinal cortex. Place cells generally fire in a single or few locations within the environment, independent of the animal's head direction in the open field. These cells are found in the dentate gyrus, CA3, and CA1 of the hippocampus.

first projects to the rhinal cortices, where it is segregated into two processing streams, one for objects, through perirhinal and lateral entorhinal cortex, and the second one for space, through the postrhinal, parasubicular, presubicular, and medial entorhinal cortices. Projections from the two (lateral and medial) entorhinal streams then converge in hippocampus where conjunctive representations for memories of objects, space, and time emerge.^{5–7}

Despite the high degree of convergence toward the top of the processing hierarchy, where a large number of cortical areas provide inputs to the next processing stage,⁸ a large fraction of neurons in parahippocampal regions have specialized spatial firing patterns (Figure 1). The different cell types nonetheless converge in the hippocampus to result in the prototypical firing pattern of place cells.⁹ Place cells are active in one or few restricted areas of space,

which can range, for cells in different positions along the dorsoventral axis, from 30 cm to several meters.¹⁰ Despite the feature of predominantly firing in a particular place, functional diversity may nonetheless persist in place cells because they can flexibly switch to non-spatial firing patterns¹¹ or, more commonly, to different levels of average firing within the place field.¹² We first describe the different cell types with spatial and directional firing patterns in the entorhinal cortex and hippocampus, and then discuss how these cell types may be functionally connected in the entorhino-hippocampal circuit.

CELL TYPES FOR SPATIAL INFORMATION PROCESSING

The cell types that have been identified as the building blocks of a network that is specialized in

spatial processing are head-direction cells, grid cells, boundary/border cells, and place cells.^{9,13,14} Cells with these firing characteristics are typically found in more than one cortical region, but each cell type is nonetheless most abundant in a particular region, for example, grid cells in the medial entorhinal cortex, head-direction cells in the presubiculum, and place cells in the hippocampus. In the following section, each of the four major cell types is described along with cell types that have closely related firing properties.

Head-Direction Cells

An example of a dedicated processing system that is well described from the early processing stages in the brainstem to the later stages in the cortex is the head-direction cell system. Head-direction cells fire at high rates when the head is oriented in a particular angular position in the horizontal plane.¹⁵ Each head-direction cell has its own preferred direction, but the distribution of preferred directions across the population of head-direction cells codes for a full 360° circle. Many head-direction cells exhibit remarkably precise tuning. For example, a cell can fire up to 100 spikes per second when the head is positioned in the preferred direction and can completely cease its firing after the head has been turned less than 40° to the left or right. Head-direction cells are already apparent on postnatal day 14 in the rat, during the animal's first independent movements away from its mother,^{16,17} and thus these properties seem to be innately encoded. Between environments, the direction-selective response of each cell is maintained, and while the entire head-direction system may reorient, all cells retain their directional tuning preferences relative to each other.¹⁸

Head-direction coding emerges from transforming vestibular information to head-direction coding throughout a series of brain stem nuclei, including the dorsal tegmental nucleus of Gudden¹⁹ and the mammillary nuclei.²⁰ The head-direction coding is then forwarded to the anterior thalamic nucleus,²¹ to the presubiculum,¹⁵ the parasubiculum, the medial entorhinal cortex,²² the retrosplenial cortex,²³ and the dorsal striatum.²⁴ In the anterior thalamic nucleus, most cells are head-direction cells, while in cortical areas, head-direction selectivity is found in a subpopulation of the neurons within each area.¹⁸

Important for their potential contribution toward generating a representation of space, the responses of some head-direction cells are modified by the speed of the animal's movement. Such velocity modulated head-direction cells occur along with a cell type that codes for translational speed alone.²⁵ Together these cells therefore code speed and

direction—the necessary components for generating a vector that represents the animal's movement in space. In addition to being locally available in cortical areas in which head-direction cells are found, the movement vector is also provided to the hippocampus by direct projections from entorhinal head-direction cells.^{26,27}

Grid Cells

In a subset of the cortical areas that contain head-direction cells, including the medial entorhinal cortex,¹⁴ the presubiculum,²⁸ and the parasubiculum, three cell classes with spatially periodic firing patterns have been identified.^{14,22,29} The first of these cell types, grid cells, fire whenever the animal is positioned at a spatial location that is part of a hexagonal lattice across the surface of the environment. Grid cells fire at the lattice positions irrespective of the animal's direction of movement or head direction.¹⁴ The second type of cells are conjunctive grid-by-head-direction cells, which fire in the same spatial pattern as grid cells, but with their firing conditional on the animal facing a particular head direction.²² The regions in which the conjunctive cells have been found are the medial entorhinal cortex, the presubiculum, and the parasubiculum. The directional selectivity of these cells can range from narrowly to broadly head-direction tuned. The least head-direction-dependent conjunctive cells may be indistinguishable from grid cells and, in cortical areas with conjunctive cells, grid cells without directional selectivity could thus belong to a continuum of conjunctive cells. However, conjunctive cells are absent in layer II of medial entorhinal cortex, which suggests that, at least in this layer, the nondirectional grid cells comprise a separate cell class.²² The third cell type with periodic spatial firing patterns are stripe cells. They have regularly spaced bands of high firing within an environment. These cells have been reported to occasionally also exhibit grid patterns, and their spatial firing pattern may thus be a special instance of the periodic firing that is exhibited by grid cells.²⁹

For grid cells and conjunctive grid-by-head-direction cells, the periodicity is a feature that is independent of the environment in which the cells are recorded. The gridness and spacing between grid peaks are maintained across environment. Furthermore, grid cells and conjunctive cells are arranged in modules within the medial entorhinal cortex, such that cells with similar spacing are adjacent to each other. Across environments, rotations and realignment are typically coherent within modules but the degree of rotation and the translational shift can differ between modules. Moreover, grid cells often show

an initial expansion or compression of their grid spacing when a familiar environment is expanded or compressed.^{30,31}

Boundary/Border Cells

An additional class of spatially selective cells in cortical association areas is comprised of boundary cells and border cells. Boundary cells form a firing band at a fixed distance from a prominent environmental boundary, such as a wall or a table edge. Border cells fire directly at the border or wall of an environment. The existence of these cell types was initially predicted based on theoretical models that proposed that place fields are generated from band-like activity patterns that intersect at a particular place.^{32,33}

Boundary/border cells have been found in the medial entorhinal cortex,³⁴ the presubiculum, the parasubiculum,²⁸ and the subiculum.³⁵ For these cells, the addition of a new wall within an environment will result in the emergence of additional firing fields at the characteristic distance from the new boundary. The boundary vector cell response therefore differs from that of grid cells, because grid cells continue to fire in a hexagonal lattice rather than directly aligning to multiple wall positions.¹⁴

Place Cells

In the dentate gyrus, the hippocampal CA3 area, and the hippocampal CA1 area, the spatial responses of most principal (excitatory) cells identify them as place cells,^{1,9} which fire when an animal is in one or a few particular locations (place fields) within its environment. If there are multiple place fields, as is common for cells in the dentate gyrus, they are arranged in a random pattern as opposed to the regular pattern of grid cells' preferred spatial locations.^{36–38} The restricted spatial firing of place cells can be further modified by the direction of an animal's movement,³⁹ by the prior context, and even by anticipated responses or paths.^{40–42} Importantly, place cells that are first recorded with a full complement of sensory inputs (e.g., visual, somatosensory, proprioceptive) can be retained when only a subset of these inputs is later available.¹ Furthermore, if a subset of sensory inputs is made unreliable, the less reliable inputs have diminished control over place cell firing.⁴³

Cells that Respond to Non-Spatial Task Features

The firing of most neurons in the rodent hippocampus and of many neurons in the parahippocampal cortices codes for aspects of the environment in a polar or

Cartesian coordinate system. In addition, there are neurons in these regions that show diverse responses to discrete features of the environment, in particular in complex tasks in which all behaviorally relevant features are represented. For example, neurons in perirhinal cortex and lateral entorhinal cortex respond selectively to individual odors⁴⁴ or visual items,⁴⁵ and many neurons in the hippocampus respond selectively to environmental features such as odors⁴⁶ or the particular sample or choice phase of a memory task.⁴⁷

Distribution of Cell Types in the Entorhino-Hippocampal Circuit

As described above, head-direction cells, grid cells, conjunctive cells, boundary vector cells, and non-spatial cells are intermingled in the parahippocampal regions, although one or more cell types are absent from some areas or layers within an area (see Figure 1). Notably, the different spatial cell types are most prevalent in the medial division of the entorhinal cortex and in those areas of the parahippocampal regions that have dense connections with the medial entorhinal cortex such as the septal presubiculum and the parasubiculum.^{28,48} Much less spatial coding is observed in the lateral division of the entorhinal cortex, consistent with its known role in non-spatial processing.^{49,50}

In the dentate gyrus and in the hippocampal CA areas, the specialized cell types that are found throughout higher cortical association areas up to the entorhinal cortex are replaced by a much lesser diversity of cells, and the prototypical hippocampal cell is thus the place cell. The loss of diversity in the hippocampal firing patterns is not the consequence of projections to the hippocampus from only a subset of the entorhinal cell types. All cell types in the entorhinal cortex are known to provide inputs to the hippocampus.²⁷

Despite the diverse inputs to the hippocampus, many recent models of hippocampal firing pattern have proposed that place cell firing arises from the convergence of grid cells with different spatial spacing onto each hippocampal principal cell.⁵¹ These models are consistent with the high proportion of grid cells in the medial entorhinal cortex,²⁸ and with the finding that grid cells in the superficial layers of entorhinal cortex project to the hippocampus.²⁷ However, functional physiological data suggest that the spatial periodicity of grid cells is not a prerequisite for sustaining place fields.^{16,52} We therefore first describe standard feedforward models of place field formation that are based on the anatomical connectivity and then contrast these models with those that include a prominent role of parallel and feedback projections.

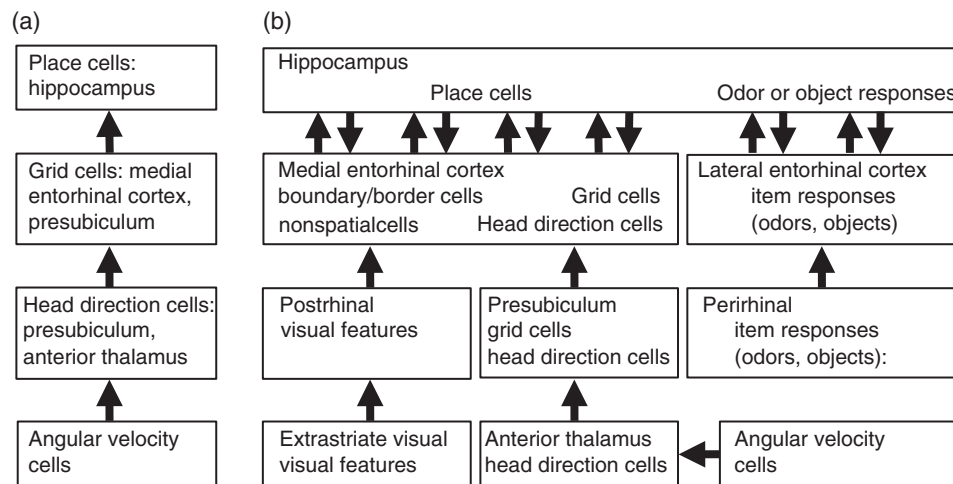


FIGURE 2 | Feedforward and parallel models of place cell firing. (a) Feedforward models. Top to bottom: Models of place cells have shown how place cell firing fields could arise from the feedforward influence of grid cells with different spatial scales and spatial phases.^{57,60} Models of grid cells have shown how grid cell firing fields could arise from integrating head-direction inputs in combination with either oscillatory interference or attractor dynamics within entorhinal cortex.^{60,61,64} Models have shown how head-direction cells could arise from input from angular velocity cells. (b) Possible parallel networks contributing to spatial processing. In addition to the feedforward circuit shown in (a), parallel systems through the entorhinal cortex are shown. For example, place cells in the hippocampus may arise from the inputs of boundary cells in the medial entorhinal cortex, as proposed by the model of boundary vector cells.^{32,33} These boundary vector cells may arise from visual features coding the distance and angle to boundaries in the environment. On the right, odor and object responses found in the hippocampus may arise from representations of odors and objects coded in the lateral entorhinal cortex. In addition to feedforward influences, feedback connections from the hippocampus to the entorhinal cortex may play an important role in updating and aligning the representations of locations by grid cells and boundary vector cells, as well as in updating the context of odor and object responses.

FEEDFORWARD MODELS

Standard Feedforward Model

Early theories of the mechanisms of place cell responses focused on a standard convergent, feedforward model in which sensory features of the environment are encoded in the cortex and drive spatially selective responses of place cells in the hippocampus.^{53–55} These models resemble the early feedforward model of visual cortex responses proposed by Hubel and Wiesel, in which feedforward input from center-surround responses in thalamus was proposed to converge to generate simple cell responses in visual cortex, and feedforward input from simple cells was proposed to converge to generate complex cell responses.⁵⁶ The recent discovery of grid cells prompted another set of feedforward models, in which convergence of feedforward input from grid cells onto a downstream hippocampal cell generates place cell responses.^{57–60} Other models have proposed that the properties of grid cell responses could themselves arise from the feedforward influence of speed-modulated head-direction cells,^{61–64} and models of head-direction cells describe how their responses could arise from convergent input of angular velocity cells.^{65–67} This work therefore suggests a feedforward hierarchical progressing from

angular velocity cells to head-direction cells to grid cells to place cells, as shown in Figure 2.

Challenges to Feedforward Models

Although hierarchical, feedforward models have many appealing characteristics, recent data challenges the view that convergent input from grid cells drives place cells. Developmental data indicates that the characteristic properties of place cells may mature prior to those of grid cells.^{16,17} These studies have shown that, in young rats that have just become able to move through an environment, place cells appear to show more accurate spatial tuning than grid cells.

Furthermore, the hard-wired nature of the grid cell network, evidenced by the fixed relative field locations between co-recorded grid cells across environments, does not easily explain the generation of orthogonal hippocampal spatial maps for new environments without additional complexities. However, recent findings show that grid cells are organized in modules, one for each spatial scale. It could thus be predicted that a slight rotation or translation of grid modules with respect to each other could result in global remapping in the hippocampus, but these data are currently only correlational and the direction

of the effect could also be opposite, from place cells to grid cells.^{2,31,68}

An additional major challenge to feedforward models comes from recent data showing a dramatic disruption of grid cell spatial periodicity during pharmacological inactivation of the medial septum.^{52,69} The pharmacological inactivation causes a loss of theta rhythm oscillations in the entorhinal cortex, which is accompanied by a loss of the characteristic hexagonal firing pattern of grid cells in medial entorhinal cortex. Some grid cells retain weak spatial selectivity, but without periodicity and not at the location of one of the former grid peaks. During the loss of grid cell spatial periodicity and when the spatial firing patterns of grid cells have become entirely different from their previous configuration, place cells retain spatially selective firing at their original location.⁵² These data suggest that sustaining place cell firing in familiar environments does not depend on the convergence of grid firing patterns onto place cells. Preliminary evidence suggests that it is even possible to generate new place cell maps in a novel room during septal inactivation.⁷⁰ These data challenge the standard hierarchical feedforward model for generation of place cell responses from grid cells, and suggest that the spatially selective response properties of neurons may arise from parallel functional pathways. Such functional and anatomical segregation into parallel circuits is also a general organizational principle of pathways in the visual system, somatosensory system and basal ganglia (see Boxes 1 and 2).

BOX 1

PARALLEL PROCESSING IN THE VISUAL SYSTEM

Within the visual system, combined anatomical and physiological data suggests that a specific subset of retinal ganglion cells (midget cells) give rise to the parvocellular pathway, which provides input to specific layers of the lateral geniculate nucleus (LGN) that project to layer 4C β of primary visual cortex.⁷¹ In contrast, a different subset of ganglion cells (parasol cells) give rise to the magnocellular pathway, which provides input to layers of the LGN that project to layer 4C α of visual cortex. Neurons in the primary visual cortex which are responsive to different visual features then show different probabilities of projections to different functionally specialized higher regions, which selectively process spatial location and object identity.⁷² The 'where' stream includes

processing of motion and direction in area MT and other dorsal areas, whereas the 'what' stream includes processing of color and form in more ventral areas such as V2 and V4. The perirhinal cortex and lateral entorhinal cortex of the rodent have been proposed to receive input from an analog of the ventral stream,⁵⁰ whereas postrhinal and medial entorhinal cortex have been proposed to receive input from a dorsal stream analog, though the spatial selectivity of medial entorhinal cortex could also depend on the selective input from presubiculum containing head-direction cells.²²

BOX 2

PARALLEL PROCESSING IN THE SOMATOSENSORY SYSTEM AND BASAL GANGLIA

Similar to the visual system, the somatosensory system contains parallel streams for processing of different inputs. For example, fast and slow mechanoreceptors project to different areas of primary somatosensory cortex.⁷³ Within the basal ganglia, data supports multiple parallel anatomical loops processing different modalities of information from frontal cortex through the basal ganglia and thalamus and back to the same specific frontal areas.^{74–76} These loops include different parallel circuits arising from motor, oculomotor, prefrontal associative, and limbic (anterior cingulate) areas and projecting through different dorsal to ventral locations in the striatum. The parallel function of these loops is supported by the selective disturbance of specific behaviors associated with damage to these different parallel anatomical circuits.⁷⁵

A further challenge to a strict feedforward model from grid cells to place cells is the finding that muscimol inactivation of the hippocampus also disrupts the spatial periodicity of grid cells.⁷⁷ These data suggest that feedback projections from the hippocampus to layers of the entorhinal cortex are critical for maintaining the spatial regularity of the grid cell firing fields. However, the hippocampal inactivation could also have an indirect effect on grid cells. Entorhinal theta oscillations gradually decreased in amplitude after hippocampal inactivation until they reached approximately 50% of the baseline value. This level of theta reduction corresponds to the threshold below which grid cells are no longer

observed after septal inactivation.^{52,69} Remarkably, the gradual time course of theta reduction after hippocampal inactivation matched the time course of the decrease in grid firing more closely than the much more rapid decrease in hippocampal firing rates.⁷⁷ It thus remains to be identified whether the effects of hippocampal inactivation on grid cells are a consequence of the loss of direct excitatory inputs to the deep layers of medial entorhinal cortex or whether the effect is rather mediated indirectly through the silencing of medial septal neurons by the hippocampal inactivation.

PARALLEL INPUT MODEL

Anatomical Evidence of Parallel Circuits

The parahippocampal regions contain several parallel anatomical pathways that run from neocortical structures through the hippocampus and back (Figure 3). One such pair of parallel pathways passes through either the medial or lateral divisions of entorhinal cortex. Inputs from postrhinal cortex contact medial entorhinal cortex, which then projects to the regions of CA1 proximal to CA3 and regions of the subiculum distal to CA1.^{78,83} These areas of CA1 and subiculum project back to the medial entorhinal cortex either directly or via the pre- and parasubiculum. In the parallel pathway, input from perirhinal cortex primarily enters the lateral entorhinal cortex, which projects to the regions of CA1 distal to CA3 and regions of subiculum proximal to CA1, which then project back to lateral entorhinal cortex. In the rodent, the two pathways are further distinguished by highly selective inputs from presubiculum to all layers of the medial but not lateral entorhinal cortex.⁴⁸

Another set of parallel pathways are organized along the dorsal to ventral axis of the medial and lateral entorhinal cortex. The dorsal entorhinal cortex projects to dorsal regions of the hippocampus, whereas the ventral entorhinal cortex projects to more ventral regions of the hippocampus.⁸⁴ A further anatomical division concerns the separate pathways from entorhinal cortex layer II to hippocampal region CA3 and from layer III to hippocampal region CA1.^{48,83} Place cell responses in regions CA3 and CA1 show remarkably similar properties, but demonstrate some differences in their remapping in response to environmental changes.^{85,86} The similarity between place fields in the different hippocampal subregions arises despite the functional differences between their direct inputs from entorhinal cortex. For example, conjunctive cells exist in layer III but not in layer II,²²

yet the place fields in their target regions, CA1 and CA3, have properties that are not distinguishable.⁸⁵

Parallel Inputs to Place Cells

In addition to the anatomical data for parallel inputs from the medial entorhinal cortex to the hippocampus,²⁷ physiological data suggests that the firing of hippocampal place cells can emerge from parallel inputs, in particular from inputs other than grid cells. As described above, place cells are formed in advance of well-defined grid cells during development,^{16,17} and place cells are retained after the disruption of the grid cell firing pattern.⁵²

How are place cells generated if not from grid cells? Before the discovery of grid cells,¹⁴ models that addressed how place cells may be formed and how they shift to different locations during manipulations of the environment⁸⁷ proposed the existence of boundary vector cells.^{32,33} This theoretical prediction has now been confirmed by recording from this cell type in brain regions that are connected to the hippocampus.^{34,35} The existence of boundary/border cells suggests possible parallel pathways of these cells or other entorhinal cell types for activating place cells. This does not exclude the possibility that grid cells can, in some circumstances, exert a prominent effect on hippocampal firing patterns. However, if different sets of cells can interchangeably provide inputs that result in consistent spatial firing patterns, there needs to be a mechanism that associates the different types of inputs with each other. Because all spatially selective cell types are intermingled within the medial entorhinal cortex, the organization could occur by direct strong associations between subpopulations of head-direction, grid, and boundary/border cells. Alternatively, the emergence of functional connectivity between different cell classes may require feedback projections from the hippocampus and thus processing throughout the entire entorhino-hippocampal loop. There are currently not enough combined studies with anatomical and physiological data to determine whether the parallel functional pathways predominantly interact within the medial entorhinal cortex or whether hippocampal projections to the entorhinal cortex co-activate the different cell classes in medial entorhinal cortex through feedback projections.

Feedback from Place Cells to Entorhinal Cortex

While it is currently not known whether feedback projections of place cells co-activate different entorhinal cell types, it has been shown that medial entorhinal

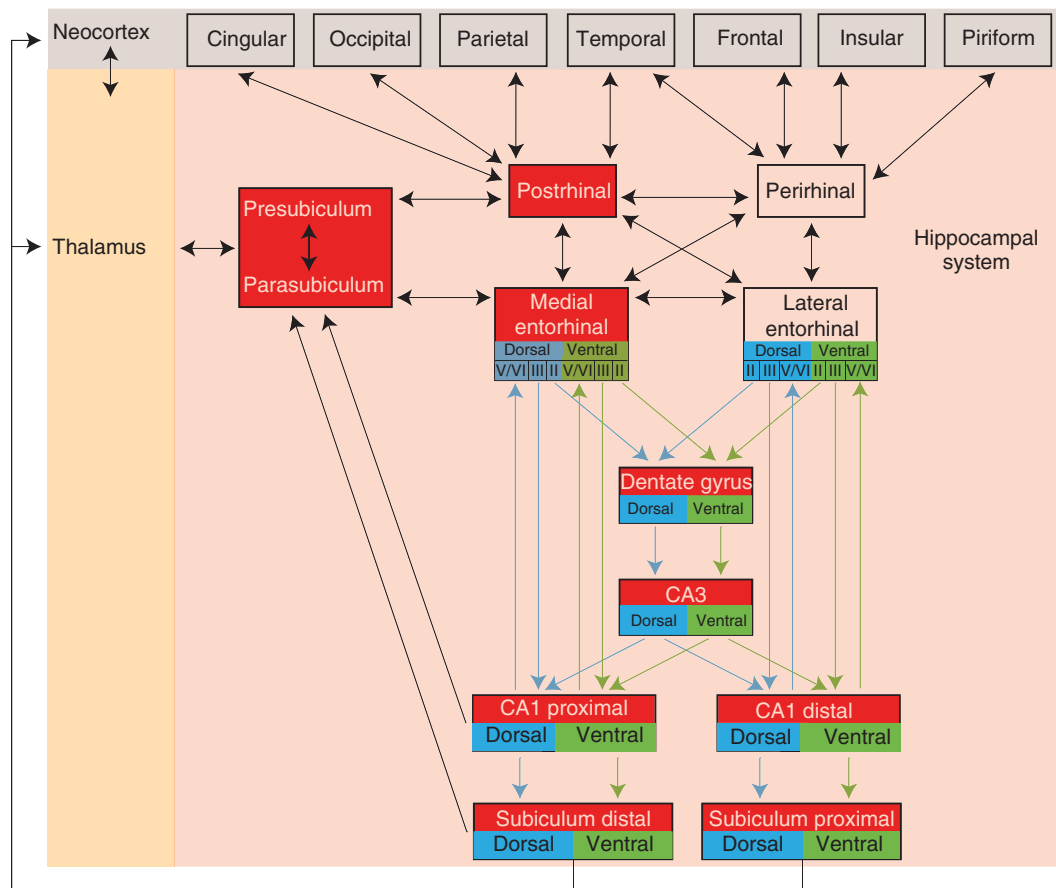


FIGURE 3 | Main connections between rodent higher association cortices. The parahippocampal region includes the perirhinal and postrhinal cortices, the medial and lateral areas of the entorhinal cortex, the pre- and parasubiculum, and the hippocampal formation includes dentate gyrus, CA3, CA1, subiculum. Extrinsic connections with other areas in the neocortex and thalamus are also represented. The arrows indicate strong to moderate connections between regions based on anatomical studies using retrograde and anterograde tracers (see Refs 78–81). In the hippocampal system, regions highlighted in red contain large proportions of spatially modulated cells such as place cells in the hippocampus and grid cells, head-direction cells, and boundary cells in parahippocampal regions. In the postrhinal cortex, cells with a broad spatial selectivity were described.⁸² The neocortical regions are defined as in Ref 79. Neocortical regions project to parahippocampal cortices, in particular to the postrhinal and perirhinal cortices in a relatively segregated way: cingulate, parietal, occipital, and temporal regions provide input to the postrhinal cortex while temporal, frontal, insular, and piriform regions project to the perirhinal cortex. Both postrhinal and perirhinal cortices give rise to strong backprojections to their neocortical afferent regions. Classically, efferent connections from the postrhinal and perirhinal cortices were described to target the medial and lateral subdivisions of the entorhinal cortex, respectively. However, the postrhinal cortex also projects to the lateral entorhinal cortex (LEC), but to a lesser extent than to the medial entorhinal cortex (MEC), and the perirhinal cortex targets both LEC and MEC in a similar way. Connections are also found between postrhinal and perirhinal cortex as well as between MEC and LEC. In addition, the postrhinal cortex and MEC are strongly interconnected with the pre- and parasubiculum, which receive projections mainly from the thalamus. Projections from MEC and LEC provide the main cortical input to the hippocampus. These projections, which form the perforant path, arise from the superficial layers of the entorhinal cortex (layer II and III) and are topologically organized. Layer II projects to the dentate gyrus and CA3 while layer III projects to CA1. In the dentate gyrus and CA3, projections from MEC and LEC converge to the same neurons. However, in CA1 and the subiculum, there is a clear segregation of medial and lateral inputs in the transverse axis: MEC projects predominantly to proximal CA1, which connects to the distal subiculum, and LEC projects predominantly to distal CA1, which connects to the proximal subiculum (proximal and distal indicate relative proximity to CA3). MEC and LEC also project directly to their respective target regions in the subiculum (not depicted). CA1 and subiculum reciprocate the connections with MEC and LEC and target the deep layers (V and VI). The subiculum receives the main output of the hippocampal system and projects to the thalamus and the neocortex. In addition, projections from the entorhinal cortex to the hippocampus are organized along its longitudinal axis such that the dorsal band of the entorhinal cortex projects to dorsal part of the hippocampus (blue) and the ventral band of the entorhinal targets ventral regions of the hippocampus (green). At every level of the hippocampal system, there are strong backprojections to the afferent regions. Even in the hippocampus, the unidirectional polysynaptic circuit (dentate gyrus to CA3 to CA1) has been reconsidered based on evidence of projections from CA3 to the dentate and from CA1 to CA3 (not depicted). Roman numerals refer to cortical layers.

grid cells depend on hippocampal place cell firing.⁷⁷ From these data, it therefore appears that the feedback from place cells to grid cells is more prominent than the influence of grid cells on place cells. In a computational model that suggested that grid cells properties are based on the integration of a velocity signal from head-direction cells, the feedback connections were proposed to play an important role.⁶¹ According to the model, the integration of velocity causes a build-up of error in the grid cells that requires the cells to be updated or reset by information from cells that are locked to sensory cues in the environment, such as place cells. Furthermore, changes to environmental dimensions cause a corresponding shift in both place field size and the spacing of grid fields, which has been interpreted as evidence of hippocampal feedback to entorhinal cortex.³⁰ Thus, the anatomical feedback connections from hippocampal place cells to the entorhinal cortex, shown in Figure 3, may play an important error-correction role to maintain the spatial specificity and the consistent alignment of grid cell firing with landmarks (see also Figure 2(b)).

Dorsal to Ventral Axis

Physiological evidence also supports parallel circuits arising from different dorsal to ventral positions in the entorhinal cortex. Grid cells in the dorsal entorhinal cortex exhibit narrow spacing between small firing fields,^{14,22} whereas grid cells in ventral entorhinal cortex show progressively larger spacing between larger firing fields^{14,22} with several meters between firing fields in neurons from the most ventral regions.⁸⁸ The scaling appears to show discrete, quantal shifts in spacing that include some overlap of parallel scales along the dorsal to ventral axis of the medial entorhinal cortex.^{30,31} The dorsal to ventral axis of the medial entorhinal cortex projects to different dorsal (septal) to ventral (temporal) regions of the hippocampus, and place cells in the hippocampus show a corresponding scale with a small size of firing fields for place cells in dorsal hippocampus and a dramatically larger size of firing fields for place cells in ventral hippocampus.^{10,89} These physiological differences have been linked to behavioral data suggesting a stronger role of dorsal hippocampus in spatial memory tasks requiring local representations,^{90,91} in contrast to a role of ventral hippocampus in regulating fear and anxiety that might involve associations with a larger spatial context and global representations.^{90–92} These differences in spatial scale along the dorsal to ventral axis are accompanied by differences in the intrinsic cellular oscillatory or resonance properties of neurons⁹³ that could regulate the scale of integration of velocity input from the head-direction system.^{61,93}

Medial and Lateral Circuits

Parallel functional circuits have also been proposed for the medial versus lateral entorhinal cortex. The parallel anatomical circuits described above appear to correspond to a clear functional division between the spatial firing responses in medial entorhinal cortex—which include grid cells, head-direction cells, and boundary/border cells—and the lack of clear spatial firing properties in lateral entorhinal cortex.⁴⁹ Unit recording studies have shown selective responses in the lateral entorhinal cortex to discrete features such as odors⁴⁴ or firing at the location objects recently removed from the environment.⁹⁴ Lesions of the lateral entorhinal cortex do not affect the spatial selectivity of hippocampal place cells, but reduce the phenomenon of rate remapping, which may encode information about non-spatial features of the environment.⁹⁵ These systems have been proposed to provide parallel pathways for the ‘what’ (lateral) and ‘where’ (medial) aspects of episodic memory function.^{49,50,59}

The functional division of firing responses appears to be accompanied by a quantitative difference in theta rhythm oscillations. Theta rhythm oscillations are weaker in lateral entorhinal cortex,⁹⁶ and stronger in medial entorhinal cortex where their blockade by medial septal inactivation is accompanied by a loss of grid cell spatial periodicity,^{52,69} but not a loss of head-direction responses.⁶⁹ The functional division within entorhinal cortex may extend along parallel pathways to different areas of region CA1,⁹⁷ where distal CA1 receives input from lateral entorhinal cortex and shows weaker spatial specificity and weaker correlations of spatial firing with theta rhythm compared with proximal CA1 that receives input from medial entorhinal cortex.

CONCLUSION

The data summarized here indicate that even cortical regions proposed to be near the top of the hierarchy of cortical structures still contain parallel functional circuits. The hippocampus may serve to associate these parallel streams in order to link the spatiotemporal trajectory of a series of events with the events and items encountered along this episodic trajectory.^{2,59,98} Despite this convergence and even though there are strong backprojections from hippocampus to entorhinal cortex, distinct physiological responses are retained in cortical areas, such that a large variety of different cell types is observed. For example, grid cells, head-direction cells, and boundary vector cells have all been described within medial entorhinal cortex, presubiculum, and parasubiculum.

This diversity of parallel pathways might be even broader in primate association cortices, which could underlie the diversity of electrophysiological responses observed in unit recordings from nonhuman primates, with similar cell types observed in different proportions in regions including perirhinal and entorhinal cortices and the hippocampus proper.⁹⁹ Future electrophysiological studies could determine the relationship between the organization

of primate and rodent pathways, and the reliance of hippocampal responses on different parallel pathways and prior experience. Because of the diversity of spatial, directional, and velocity-related firing patterns, the investigation of neuronal coding in freely moving animals might provide key insight into parallel processing schemes that are maintained through a series of brain areas within the cortical hierarchy.

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